Journal of Pediatric Urology (2007) 3, 206—208

Journal of Pediatric urology

Natural history of testicular regression syndrome and consequences for clinical management

Paul K. Hegarty, Imran Mushtaq, Neil J. Sebire*

Department of Paediatric Histopathology, Great Ormond Street Hospital, Great Ormond Street, London WC1N 3JH, UK

Received 19 June 2006; accepted 11 August 2006
Available online 7 November 2006

KEYWORDS
Testicular regression;
Vanished testis

Abstract *Aims:* Testicular regression syndrome (TRS or 'vanishing testis') is a condition in which a testis is thought to have once existed but has atrophied and disappeared during early development. The natural history of TRS is in completely understood, due to the absence of any prospectively studied cohort of patients. This study aimed to quantify the cardinal features of the disease and correlate these with age.
Materials and methods: A total of 117 cases of TRS were submitted for histopathological examination. Patient age ranged from birth to 12 years, with a median age of 2 years. The proportion of each histological feature present was analysed according to age, using the χ^2 test.
Birth Results: The 117 cases accounted for 21% of the testicular/paratesticular specimens examined. Only 12 cases (10%) were found to contain testicular tissue, with no readily identifiable germ cells and in particular no atypical germ cells identified. Features such as haemosiderin-laden macrophages, calcification, the presence of a nodule, vas or epididymis were less prevalent amongst specimens from older boys.
Conclusions: This is the largest series studied to date. With only 10% of the removed specimens containing identifiable testicular tissue with no germ cells seen, a negligible risk of future germ-cell cancer on the affected side is implied. If the laparoscopic findings suggest a diagnosis of vanishing testis, we contend that a groin exploration may be no longer indicated.
© 2006 Journal of Pediatric Urology Company. Published by Elsevier Ltd. All rights reserved.

Introduction

Testicular regression syndrome (TRS) or 'vanishing testis' is a condition in which an apparently initially developmentally normal testis is thought to have once existed in fetal life and has subsequently atrophied and disappeared. The condition may be unilateral or bilateral with partial or complete absence of testicular tissue in the presence of normal external genitalia. Typically this results in a blind-ending vas and vessels with a variable amount of testicular or paratesticular tissue remaining. The current concept presumes that the initial embryological development was normal with some descent of the normal testis, followed by a catastrophic event such as torsion.

The aetiology of the TRS has a number of proposed mechanisms. Firstly, the incompletely descended testis is believed to be more susceptible to torsion in the fetal and

* Corresponding author. Tel.: +44 0207 829 8663; fax: +44 0207 829 7875.
E-mail address: sebirn@gosh.nhs.uk (N.J. Sebire).

1477-5131/$30 © 2006 Journal of Pediatric Urology Company. Published by Elsevier Ltd. All rights reserved.
doi:10.1016/j.jpurol.2006.08.007

perinatal period. This is evidenced by the presence of haemosiderin-laden macrophages in surgically removed specimens [1], consistent with the venous congestion that occurs with haemorrhagic infarction secondary to torsion of a structure. Conversely, trauma to the intrascrotal testis perinatally has been proposed [2]. Earlier descent of the left testis may account for the predilection for this side. Finally, a genetic abnormality, such as microdeletion of the Y chromosome, has been seen associated with observed regression of testicular tissue [3] and boys with persistence of Müllerian duct structures have been observed to undergo TRS after birth [4]. If the process occurs late in the pregnancy then a virilized boy results. Early loss of both testes antenatally can lead to an infant being born with features of intersex [5]. We have already described the pathogenesis of TRS [6].

The natural history of TRS is not completely understood. The rate of shrinkage is not clearly defined due to the absence of any prospectively studied cohort of patients with this condition. As the testis shrinks, the cellular response of the surrounding tissue may give some indication as to the pathogenesis of TRS. Finally, in managing such cases the patient and physician must be confident of the natural history, especially regarding the malignant potential of any testicular tissue remaining on that side.

This study analysed all specimens of TRS submitted for histopathological examination at a tertiary referral paediatric hospital with the aim of defining the natural history of the vanishing testis in terms of pathological features present, with particular regard to implications for clinical management.

Methods

Between 1988 and 2004, 117 specimens from cases of TRS were submitted for histopathological examination. The patient population ranged from neonates to 12 years of age, with a median age of 2 years. All cases were made anonymous for the purpose of the study. The histological features were reviewed including the size of the macroscopically visible nodule if present, and microscopic features such as presence of testicular and paratesticular structures, as well as haemosiderin-laden macrophages and foci of dystrophic calcification. A spermatic cord structure was deemed present when a component such as an artery or venous plexus was identified. These features were categorized relative to the age of the patient. The proportion of each feature present according to age was analysed using the χ^2 test. The study was approved by the local Research Ethics Committee.

Results

The 117 cases accounted for 21% of the testicular/paratesticular specimens examined during the given time interval. In 71 cases (61%) a vas was identifiable, whereas a spermatic cord was found in 43 cases (37%). Eighty-five cases (73%) had either vas or spermatic cord present. In 39 (33%) epididymal structures were present and in 52 (44%) there was a macroscopically visible distinct nodule, ranging in size from 1 to 20 mm in diameter, with a median of 5 mm. Of the 117 cases, only 12 cases (10%) were found to contain residual identifiable testicular tissue containing seminiferous tubules. In these, residual islands of tubules were found within an area of fibrotic stroma (Fig. 1). Routine morphological examination of the tubules present did not identify any recognisable germ cells, and in particular no atypical germ cells were seen. There was no association between the finding of a macroscopic nodule and the presence of testicular tubules on microscopic examination. In 21 cases (18%) there was no identifiable spermatic cord, vas, epididymis or macroscopic nodule, the specimen consisting of predominantly fibrous tissue, with or without haemosiderin-laden macrophages and dystrophic calcification (Figs. 2 and 3).

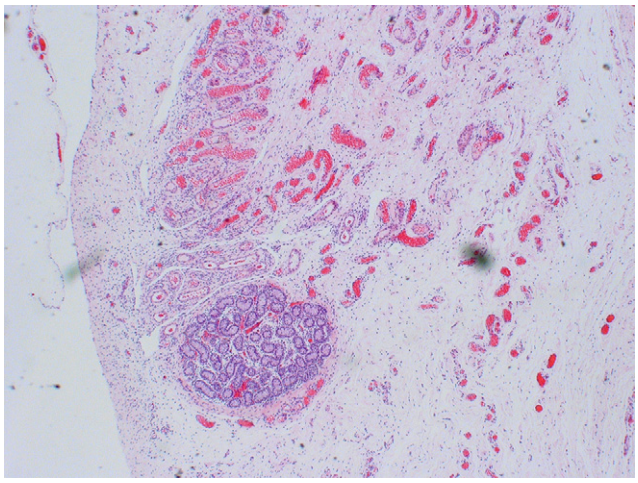

Figure 1 Photomicrograph of a case of TRS demonstrating fibrous tissue with a small residual cluster of seminiferous tubules. No germ cells are identified (H&E, original magnification $\times$40).

When analysed according to age a number of histological features were less frequently identified in the resected specimens from older boys. Using age cut-offs for each year of life, the proportion with the lowest *P*-value on the χ^2 test for each feature is shown in Table 1. The age when these features tend to disappear from the specimens varies according to the feature. The most statistically significant

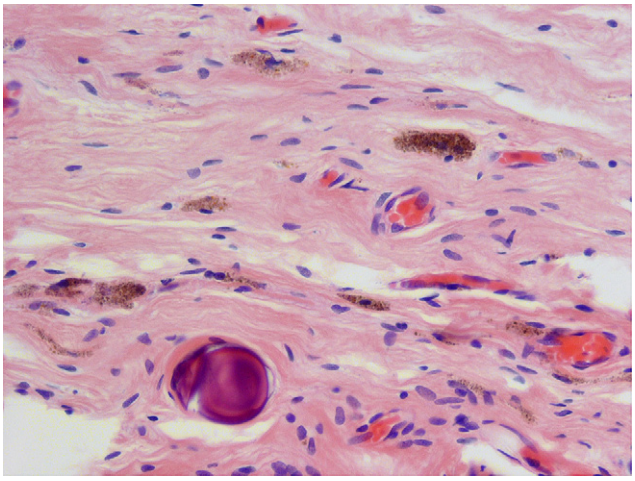

Figure 2 Photomicrograph of a case of TRS demonstrating fibrous tissue with scattered foci of dystrophic calcification and numerous haemosiderin-laden macrophages (H&E, original magnification $\times$250).

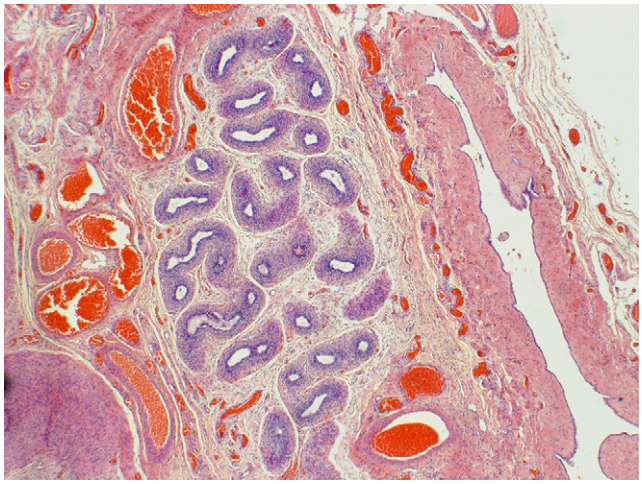

Figure 3 Photomicrograph of a case of TRS demonstrating no identifiable testis but epididymal and spermatic cord structures (H&E, original magnification ×20).

age cut-offs were found to be 2 years for haemosiderin-laden macrophages, 3 years for dystrophic calcification, 5 years for the presence of a nodule and the vas, and 6 years for epididymal remnants.

Discussion

The aim of this study was to investigate the macroscopic and histopathological findings in patients with TRS in relation to patient age with a view to greater understanding of the natural history of the condition. Specific details of the histopathological findings in this condition have been previously reported [6]. We describe boys from newborn through to prepubertal age. The most striking result is that only 10% of specimens contained any identifiable testicular tubules. These consisted mainly of Sertoli cells enveloped in fibrous strands. This would indicate that any exocrine function was impossible and endocrine function unlikely. Of more clinical relevance, is the absence of readily identifiable germ cells, and that no specimen contained morphologically atypical germ cells. It has been suggested that testicular malignancy develops in genetically abnormal testes or in testes exposed to an abnormal environment rather than failure of descent in itself being responsible for any associated increase in risk [7]. Further, review of the literature has not identified any report of testicular germ cell tumours apparently arising from known TRS. In conjunction with the present data, these findings suggest that TRS is highly unlikely to predispose to future malignant transformation.

Table 1 Proportion of specimens containing feature according to age

	Age	Proportion	Age	Proportion	*P*-value
Haemosiderin	0–2	85%	>2	58%	0.02
Calcification	0–3	52%	>3	24%	0.02
Nodule	0–5	46%	>5	21%	0.06
Vas	0–5	65%	>5	44%	0.11
Epididymis	0–6	35%	>6	8%	0.07

Our finding of haemosiderin-laden macrophages being present in about two-thirds of cases is similar to other series, which report frequencies ranging from about 40% to 90% [1,8]. This pattern is less prevalent amongst older boys, but the majority still display this feature despite an interval of several years since the initial presumed insult. Macrophages represent the late cellular response to tissue damage and elimination of haemosiderin may be incomplete even after many years, a feature also recognised at other sites. Other histological features observed less frequently amongst older boys are the presence of calcification, a macroscopic nodule, vas and epididymis. These data thus further imply that there is probably a gradual resorption of residual structures throughout childhood. The spermatic cord structures, however, appear relatively preserved even in older boys, which probably represents sparing of the cord proximal to the site of torsion.

The absence of any identifiable testicular or cord structures in 18% of cases submitted for histopathological examination may be due to the surgeon failing to locate the atrophied nodule or could simply represent cases that had undergone complete atrophy. This potential outcome should be discussed in counselling the parents of any boy with possible TRS prior to surgery.

In conclusion, the results of this study have demonstrated that histopathological examination of removed tissue from cases of TRS identifies testicular tissue in only 10%. Furthermore, as germ cells are not readily identifiable within these tissues, this implies a negligible risk of future germ-cell malignancy, in keeping with current understanding of the pathogenesis of testicular neoplasia. In the modern era of minimally invasive surgery, most boys presenting with an impalpable testicle will undergo diagnostic laparoscopy. If the laparoscopic findings suggest a diagnosis of TRS, the current clinical question is whether a groin exploration should be carried out to identify and remove any remaining testicular tissue; on the basis of these data, we suggest not.

References

[1] Smith NM, Byard RW, Bourne AJ. Testicular regression syndrome—a pathological study of 77 cases. Histopathology 1991;19:269–72.
[2] Sutcliffe JR, Wilson-Storey D, Smith NM. Ante-natal testicular torsion: only one cause of the testicular regression syndrome? J R Coll Surg Edinb 1996;41:99–101.
[3] Calogero AE, Garofalo MR, Barone N, De Palma A, Vicari E, Romeo R, et al. Spontaneous regression over time of the germinal epithelium in a Y chromosome-microdeleted patient: case report. Hum Reprod 2001;16:1845–8.
[4] Imbeaud S, Rey R, Berta P, Chaussain JL, Wit JM, Lustig RH, et al. Testicular degeneration in three patients with the persistent mullerian duct syndrome. Eur J Pediatr 1995;154:187–90.
[5] Rattanachaiyanont M, Phophong P, Techatraisak K, Charoenpanich P, Jitpraphai P. Embryonic testicular regression syndrome: a case report. Med Assoc Thai 1999;82:506–10.
[6] Law I, Mushtaq M, Wingrove K, Malone M, Sebire NJ. Histopathological features of testicular regression syndrome: relation to patient age and implications for management. Fetal Pediatr Pathol 2006;25:119–29.
[7] Asklund C, Jorgensen N, Kold Jensen T, Skakkebaek NE. Biology and epidemiology of testicular dysgenesis. BJU Int 2004;93:6–11.
[8] Grady RW, Mitchell ME, Carr MC. Laparoscopic and histological evaluation of the inguinal vanishing testis. Urology 1998;52:866–9.